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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER
PARAS JR, PETER

ART UNIT	PAPER NUMBER
1632	20

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/349,925	Applicant(s) CHANGEUX ET AL.	
	Examiner Peter Paras	Art Unit 1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 May 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *40-47 and 51-62* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *40-47 and 51-62* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☒ Interview Summary (PTO-413) Paper No(s). *20* .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

The previous Office action mailed on 7/3/02 is hereby vacated in view of the instant Office action.

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on May 6, 2002 has been entered.

Claims 40-41, 43-44, 46-47, 54-55, and 58 have been amended. New claims 59-62 have been added. Claims 48-50 have been cancelled. Claims 40-47 and 51-62 are pending and are under current consideration.

Information Disclosure Statement

It is noted that the IDS received on 10/03/00 has not been considered. It is further noted that Applicants have indicated that the references cited in the IDS were to be found in parent applications 08/465,712 and 08/358,627. Currently, the parent applications are not available. When the parent applications become available the Examiner will consider the IDS.

Drawings

New formal drawings are required in this application because the previously submitted drawings were objected to by the Draftsman pursuant to 37 C.F.R. 1.84 or 1.152. See the PTO form 948 attached to the Office action mailed on 9/28/00. Applicant is advised to employ the services of a competent patent draftsperson outside the Office, as the Patent and Trademark Office no longer prepares new drawings. The corrected drawings are required in reply to the Office action to avoid abandonment of the application. The objection to the drawings will not be held in abeyance.

Claim Rejections - 35 USC § 112, 1st paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 40-47, 51-52 and 55-62 as originally filed, amended, or newly added are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The previous rejection is maintained for the reasons of record advanced on pages 2-5 of the Office action mailed on 6/6/01.

Applicant's arguments filed 5/6/02 have been fully considered but they are not persuasive. Applicants have argued that the transgene and the site of transgene

integration in a transgenic mouse's genome with regard to a resulting phenotype in a transgenic mouse are not relevant in determining whether the instant claims are enabled. Applicants assert the instant claims define both the promoter sequence and the nucleotide sequence encoding a polypeptide, which are present in each of the transgenic mice of the invention. In light of such Applicants submit that all of the embodiments encompassed by the claims are enabled. Applicants go on to point out that the promoter sequence is defined by the claims as being from about nucleotides (-) 1125 to (+) 38 of SEQ ID NO: 22 and that the nucleotide sequence contained within the transgene can encode an oncogenic, tumorigenic, immortalizing protein, or a reporter protein. Applicants assert that the instant specification, on pages 38-39, describes the expression pattern of a β-galactosidase reporter gene operably linked to a promoter in transgenic mice. Applicants further assert that 2 of the 3 founder transgenic mice created express the transgene demonstrating that the newly discovered promoter confers the expression pattern of the β2-subunit of the neuronal nicotinic acetylcholine receptor. See the amendment on pages 6-9.

Applicants point to Aguzzi et al and Camper et al for support that a promoter sequence can be used to express a polypeptide in a tissue specific manner. Applicants submit that the references relied upon by the Examiner, Palmiter, Kappel, and Cameron, as evidence of undue experimentation to make transgenic mice are irrelevant to the instant invention. Applicants have supported this assertion by again pointing out that the claimed promoter can direct expression of a heterologous polypeptide in neurons of a transgenic mouse. Finally, Applicants have argued that the skilled artisan

is willing to generate as many mice as it takes in order to find those that express the transgene in the desired manner. Applicants submit that such experimentation is not undue and point to Palmiter and Brinster for support; the Palmiter references teaches that the level of expression of a particular transgene varies widely from one founder animal to another and that not all transgenic mice even express a particular transgene. See the amendment on pages 9-12.

In response, the Examiner maintains that the phenotype resulting from expression of a transgene is not predictable. See the advisory action mailed o 10/11/01; the Office action mailed on 6/6/01 on pages 2-5; and the Office action mailed on 9/28/00 on pages 2-7, in particular see Palmiter, Kappel, and Cameron on page 5. More importantly, Applicants have not disclosed a particular phenotype that results from transgene expression in the claimed transgenic mice; no phenotype is recited in the claims. Although Applicants have provided a working example that demonstrates that the claimed promoter is able to direct expression of a reporter gene in a tissue specific manner, expression of a reporter gene is insufficient to enable the skilled artisan to predict any phenotype that may result from expression of oncogenic, tumorigenic, or immortalizing proteins embraced in the claims. It is also of interest to note that the claims are encompassing heterologous nucleotide sequences that encode any oncogenic, tumorigenic, or immortalizing proteins and are not limited to specific species of the recited classes of proteins. The evidence of record does not support any phenotype resulting from expression of heterologous nucleotide sequences that encode any of the broad classes of oncogenic, tumorigenic, or immortalizing proteins. It would

be highly unpredictable, in light of the evidence of record, to attempt to predict any phenotype in a transgenic mouse that may result from expression of any of the oncogenic, tumorigenic, or immortalizing proteins embraced by the claims.

As stated in the Advisory action of 10/11/01, a phenotype resulting from expression of a transgene is dependent on the particular transgene, the level of transgene expression, and the site of integration. These points are well supported by Palmiter, Kappel, and Cameron as originally recited in the Office action of 9/28/00 on page 5. [Palmiter reports that not all transgene constructs work well due to inappropriate expression patterns and inadequate expression levels; Kappel reports that inherent cellular mechanisms may alter the pattern of gene expression; and Cameron reports that [transgene] expression levels for various reasons, like the site integration for example, are unpredictable.] Applicants appear to suggest that these points are irrelevant because the skilled artisan can simply screen as many transgenic mice as it takes in order to find the mouse that displays a desired phenotype. Such a suggestion is welcoming trial and error experimentation to overcome the unpredictability of the transgenic art. It also appears that Applicants are suggesting that trial and error experimentation is not undue experimentation. A careful analysis of the Wands factors shows that 1) the **state of the transgenic art** is unpredictable with regard to the phenotype resulting from transgene expression; 2) the **claims are overly broad** with respect to polynucleotides encoding any oncogenic, immortalizing, or tumorigenic protein; 3) the instant specification has **failed to provide working examples** that correlate expression of any oncogenic, immortalizing, or tumorigenic protein with a

particular phenotype; 4) the instant specification has **failed to provide guidance** for the creation of transgenic mice that express any oncogenic, immortalizing, or tumorigenic protein; and 5) and that transgene expression is **unpredictable** at best. Moreover, Palmiter and Brinster, as cited by Applicants for support of routine screening of transgenic mice, actually made the same points as the Examiner did in supporting the argument that transgene expression is unpredictable; the Palmiter references teaches that the level of expression of a particular transgene varies widely from one founder animal to another and that not all transgenic mice even express a particular transgene. Finally, the Camper and Aguzzi references while teaching that a promoter can direct tissue specific expression of a transgene as argued by Applicants on pages 9-10 of the amendment, do not provide any relevant teachings that would overcome the unpredictable nature of transgene expression. In light of the above, Applicant's assertions that screening transgenic mice to find one that exhibits the desired phenotype, are insufficient.

Applicants have argued that the claimed promoter sequences can direct expression of a heterologous nucleotide sequence in a tissue-specific manner. Applicants further argue that these promoters sequences in combination with nucleotide sequences that encode oncogenic, tumorigenic, or immortalizing proteins can provide a novel transgenic system for directing neuron-specific tumor formation. See page 6 of the specification. Applicants have pointed to Kioussis for support of the invention as contemplated because Kioussis discusses the development of transgenic mice expressing oncogenes, which develop tumors. Applicants have also cited Gordon for

support, as Gordon has reported that transgenic mice comprising sequences encoding oncogenic, tumorigenic, or immortalizing proteins linked to tissue specific promoters developed tumors. Applicants assert that the phenotype of the claimed transgenic mice would include tumorigenesis in neurons and that the mice could be used for testing anticancer drugs or as a model for cancer. Applicants also assert that transgenic mice expressing oncogenic, tumorigenic, or immortalizing proteins could also be used for developing neuronal cell lines as suggested by the specification, Camper, and Kioussis. See the amendment on pages 12-16.

In response, the Examiner acknowledges that the claimed invention could be used for tissue-specific tumor formation, particularly in neurons, or to create cell lines if the claimed transgenic mice were enabled as claimed. The main issue is that the evidence of record has not taught the creation of any of the claimed transgenic mice expressing oncogenic, tumorigenic, or immortalizing proteins, which exhibit a phenotype. Further, as explained above the art of transgenics is unpredictable with regard to transgene expression and a resulting phenotype. As such it cannot be predicted that expression of any oncogenic, tumorigenic, or immortalizing proteins as claimed would result in tumor formation. The Examiner agrees that tumor formation is a phenotype. However, the evidence of record has not demonstrated that this aspect of transgenesis, tissue-specific tumor formation, is predictable. While the Kioussis and Gordon references may teach that some transgenic mice with tissue-specific tumors have been created, these references do not with any certainty assert that creating such mice is predictable. The Kioussis and Gordon references do not sufficiently overcome

the unpredictability of the transgenic art as discussed above and supported by Palmiter, Kappel, and Cameron (see above). Moreover, a transgenic mouse without a phenotype does not appear to have any particular use. The specification has taught that uses for mice that have a phenotype, for example drug screening for anti-tumor drugs. The working examples provided by the specification do not teach the creation of a single transgenic mouse expressing a heterologous nucleotide sequence encoding oncogenic, tumorigenic, or immortalizing proteins operably linked to the claimed promoter that develop neuronal tumors. As such the claimed transgenic mice do not exhibit a phenotype and do not have any other apparent uses. Isolation of cells from a transgenic mouse would be dependent on the creation of the actual mouse (see below). Since the claimed transgenic mice have not been created, the teachings of Camper and Kioussis, with regard to creation of cell lines from the like, are not relevant. In the absence of a disclosed phenotype, the claimed transgenic mice do not have any readily apparent uses.

It is noted that claims 46-47, 51-52, and 55-58 are directed to methods of producing a neuronal host cell that expresses a heterologous protein. Claims 46-47 and 51-52 however do not specify whether the neuronal host cell is *in vitro* or *in vivo*. For the purposes of this rejection the claims are interpreted, in light of the specification, to read on neuronal cells isolated from a transgenic mouse since the instant specification has not provided guidance or teachings for other methods of producing neuronal cells that express a heterologous protein *in vivo*. Claims 55-58 require a transgenic mouse as the source of the neuronal cells. These claims, as well as product

claims 40-45 and 59-62, recite that a DNA sequence is introduced into a mouse at an embryonic stage. The term embryonic stage does not accurately reflect the method of transgenesis used to produce the transgenic mice embraced by the claims particularly because the working examples provided on pages 35 and 38 of the specification discuss the creation of transgenic mice by microinjection of a reporter transgene into fertilized oocytes. Embryonic stages encompass multi-celled embryos. Introduction of a heterologous nucleotide sequence into a multi-cell embryo would not allow the creation of a transgenic mouse all of whose germ and somatic cells contain the heterologous nucleotide sequence as required by the claims. Rather, the resulting transgenic mouse would be chimeric, wherein some of the somatic cells would contain the heterologous nucleotide sequence and wherein it is unclear if any germ cells would contain the heterologous nucleotide sequence. Further, since all cells in a chimeric mouse would not contain the transgene it is unclear if the transgene would be expressed at a level sufficient to result in a phenotype. However, a fertilized oocyte is at the single cell stage. Because a fertilized oocyte is single celled, introduction of a heterologous nucleotide sequence into such would allow every cell in the resulting transgenic mouse to contain the heterologous nucleotide sequence. A fertilized oocyte would be appropriate for creating the transgenic mice embraced by the claims. As set forth above and for the reasons of record, these claims are not enabled as the transgenic mice are not enabled.

Accordingly, the rejection is maintained for the reasons of record and as discussed in the preceding paragraphs.

Note, a showing by Applicants of a transgenic mouse whose genome comprises a nucleotide sequence encoding a specific oncogenic, tumorigenic, or immortalizing protein, (i.e. a species of oncogenic, tumorigenic, or immortalizing proteins) operably linked to the claimed promoter that develop neuronal tumors may be sufficient to overcome the rejection.

Claim Rejections - 35 USC § 112, 2nd paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

The previous rejection of claims 43-44 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is withdrawn in view of Applicant's amendments to the claims.

The following are new grounds of rejection under 35 U.S.C. 112, second paragraph:

Claims 40-47, 51-62 as originally filed, amended or newly added are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 40, 41, 46, 55, and 59 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite in that it fails to point out what is included or excluded by

the claim language. This claim is an omnibus type claim. The claims refer to Figure 1. Correction is required. Claims 42-45, 47, 51-54, 56-58, and 60-62 depend from claims 41, 46, 55, and 59.

Claims 40, 41, 46, 55, and 59 recite the limitation "the β2-subunit of neuronal nicotinic acetylcholine receptor" in lines 2-3, lines 3-4, line 3, lines 4-5, and lines 3-4 respectively. There is insufficient antecedent basis for this limitation in the claim. There does not appear to be one β2-subunit of neuronal nicotinic acetylcholine receptor. 42-45, 47, 51-54, 56-58, and 60-62 depend from claims 41, 46, 55, and 59.

Claim 41 recites the limitation "the germ cells" in line 2. There is insufficient antecedent basis for this limitation in the claim. Claims 42-45 depend from claim 41.

Claim 43 recites the limitation "the endogenous DNA of the second mouse" in lines 1-2. There is insufficient antecedent basis for this limitation in the claim. Claim 45 depends from claim 43.

Claim 43 recites the limitation "the endogenous DNA of the first mouse" in lines 2-3. There is insufficient antecedent basis for this limitation in the claim. Claim 45 depends from claim 43.

Claim 46 recites the limitation "the heterologous polypeptide" in lines 5-6. There is insufficient antecedent basis for this limitation in the claim. Claims 47 and 51-54 depend from claim 46.

Claim 55 recites the limitation "the heterologous polypeptide" in lines 7. There is insufficient antecedent basis for this limitation in the claim. Claims 56-58 depend from claim 55.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claim 40 is provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 15 of copending Application No. 08/465,712. Although the conflicting claims are not identical, they are not patentably distinct from each other because the transgenic mice of copending Application No. 08/465,712 encompass the transgenic mice of the instant application. For example, the transgenic mice encompassed by both applications comprise a β2 neuronal nicotinic acetylcholine receptor operatively linked to a heterologous polynucleotide, wherein such is expressed in neurons of the transgenic mice. Heterologous polynucleotides that encode oncogenic, tumorigenic, or immortalizing proteins are considered to be obvious variants of the transgenic mice claimed in 08/465,712. Since the parent application is not available the Examiner is relying on the Double Patenting rejection set forth in the Office action mailed on 9/28/00 on pages 8-9.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Peter Paras, Jr., whose telephone number is 703-308-8340. The examiner can normally be reached Monday-Friday from 8:30 to 4:30 (Eastern time).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Reynolds, can be reached at 703-305-4051. Papers related to this application may be submitted by facsimile transmission. Papers should be faxed via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center numbers are (703) 308-4242 and (703) 305-3014.

Inquiries of a general nature or relating to the status of the application should be directed to Patsy Zimmerman whose telephone number is (703) 308-0009.

Peter Paras, Jr.
Art Unit 1632

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